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EXAMINER	
BASI, NIRMAL SINGH	
ART UNIT	**PAPER NUMBER**
1646	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/668,035	BEHAN ET AL.	
	Examiner	Art Unit	
	Nirmal S. Basi	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *5-7 and 17-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 8-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/22/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of Group V claims 1-4 and 8-16 on 12/20/06 is acknowledged. The traversal is on the ground(s) that it would not be a serious burden to examine groups V and VI together. This is not found persuasive because a search of groups V and VI would not be coextensive with regard to the literature search. The two methods are independent and distinct. The method of Group V is drawn to a method of identifying a ligand to an orphan receptor and the method of Group VI is drawn to a method of modulating an orphan GPCR comprising contacting the receptor with the compound identified by Group V. The assay steps of the two methods are indepent and distinct. Further there is no requirement that the same GPCR is modulated in the invention of Group VI. An examination of the materially different, patentably distinct inventions in a single application would constitute a serious undue burden on the examiner. Claims 5-7 and 8-15 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

The requirement is still deemed proper and is therefore made FINAL.

3. The disclosure is objected to because of the following informalities:

The application claims the benefit of U. S. Application No. 09/364,425. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78) as well as the relationship of instant application to the parent. The priority information must be updated. U. S. Application No. 09/364,425 is now Patent 6,653,086.

Appropriate correction is required.

4. The drawings objected to because each Figure must described separately in the Brief Description of the Drawings. Figure 12 should be labeled as Figures 12A-D, Figure 13 should be labeled as Figures 13A-D, and described separately in the Brief Description of the Drawings as Figure 12A, 12B, 12C, 12D, 13A. 13B, 13C AND 13D or the equivalent, as required by 37 C.F.R. § 1.84 Appropriate correction is required.

5. ***Sequence Rules Compliance***

This application fails to comply with the sequence rules, 37 CFR 1.821-1.825. Nucleotide and polypeptide sequences must be identified with the corresponding SEQ ID NO. Title 37, Code of Federal Regulations, Section 1.821 states "reference must be made to the sequence by use of the assigned identifier", the identifier being SEQ ID NO. Sequences in Figure18 must be identified by their corresponding SEQ ID NO:. Also application fails to comply with the Sequence Rules, 37 CFR 1.821 et seq., because claims 8 and 13 refer to orphan receptors which comprise a fusion protein, without a disclosed "SEQ ID NO:" identifier of the listed orphan receptors, the structure of the fusion protein cannot be determined. Compliance with sequence rules is required.

Claim Rejection, 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-4 and 8-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and 12 are indefinite because it is not clear what is a partial agonist, inverse agonist, and compound efficacy. Claim 2, 15 and 16 are indefinite because it is not clear what is a partial agonist and inverse agonist. Partial agonist is described in the specification as, "materials (e.g., ligands, candidate compounds) which activate the intracellular response when they bind to the receptor to a lesser degree/extent than do agonists, or enhance GTP binding to membranes to a lesser degree/extent than do agonists". Partial agonist is viewed by the examiner as a relative term which renders the claim indefinite. The term "partial agonist" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Since the designation of "partial agonist" is dependent on a comparison with agonist activity, and agonists can have different degrees of activity, the determination if a compound is a partial agonist can not be made without the baseline activity of the agonist. For example, if two agonists have arbitrary activities of 100 units and 50 units, and the test compound has an activity of 75 units, it is not clear if said test compound would be an agonist of partial agonist. Therefore, without knowledge of the agonist, the intracellular response that is being activated and the level of activation, the metes and bounds of what is considered a partial agonist cannot be determined. Further, inverse agonist is defined as, "materials (e.g., ligands, candidate compounds) which bind to

either the endogenous form of the receptor or to the constitutively activated form of the receptor, and which inhibit the base line intracellular response initiated by the active form of the receptor below the normal base level of activity which is observed in the absence of agonist or partial agonist or decrease GTP binding to membranes". Also, since the receptors used in instant method are orphan receptors which do not have a defined or known universal intracellular response, it is not clear which parameters are measured to determine if a compound is an agonist, partial agonist or partial antagonist so as to allow the metes and bounds of the claim to be determined.

As pertaining to claims 1 and 12 "compound efficacy" is defined in the specification as, "measurement of the ability of a compound to inhibit or stimulate receptor functionality, as opposed to receptor binding affinity". It is not clear what is "receptor functionality" and what parameters are inhibited or stimulated by compound interaction so as to allow metes and bounds of the claims to be determined. In particular, it is not clear what parameters are being measured and how they are related to achieve the goal set out in the preamble. Further the claims do not recite a final "candidate identification" step achieving the goal set forth in the preamble.

Claims 2 is indefinite because it is unclear what directly identifies the compound as an inverse agonist. In particular what activity is measured and what comparison is made so as to lead to the identification of a compound as an inverse agonist of an orphan receptor.

Claims 3 is indefinite because it is unclear what directly identifies the compound as an agonist. In particular what activity is measured and what comparison is made so as to lead to the identification of a compound as an agonist of an orphan receptor.

Claims 4 is indefinite because it is unclear what directly identifies the compound as a partial agonist. In particular what activity is measured and what comparison is made so as to lead to the identification of a compound as a partial agonist of an orphan receptor.

Claims 15 is indefinite because it is unclear what directly identifies the compound as an inverse agonist or an agonist. In particular what activity is measured and what comparison is made so as to lead to the identification of a compound as an inverse agonist or an agonist.

Claims 16 is indefinite because it is unclear what directly identifies the compound as an inverse agonist. In particular what activity is measured and what comparison is made so as to lead to the identification of a compound as an inverse agonist.

Claims 8 and 13 are indefinite because all the orphan receptors have not been sufficiently defined in the claims and specification so as to allow the metes and bounds of the claims to be determined. The name for each orphan receptor does not sufficiently serve to characterize said receptor. The orphan receptors listed which comprise a fusion protein, without a disclosed "SEQ ID NO:" identifier of the listed orphan receptors, the metes and bounds of the structure of the fusion protein cannot be determined.

Claims 9, 10, 11, and 14 are rejected for depending upon an indefinite base (or intermediate) claim and fail to resolve the issues raised above.

Claim Rejections - 35 USC § 101 and 35 USC § 112, 1st paragraph

The following is a quotation of 35 U.S.C. 101:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-4 and 8-16 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

A “specific utility” is a utility that is specific to the subject matter claimed, as opposed to a “general utility” that would be applicable to the broad class of the invention. A "substantial utility" is a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. A "well established utility" is a utility that is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one

skilled in the art. A "well established utility" must also be specific and substantial as well as credible.

Based on the record, there is not a "well established utility" for the claimed invention.

Claims 1-4 and 8-10 are directed to a method for directly identifying a candidate compound as a compound selected from the group consisting of an inverse agonist, a partial agonist and an agonist, to an endogenous, constitutively active G protein coupled orphan receptor, comprising the steps of: a)contacting a candidate compound with GPCR Fusion protein, said Fusion Protein comprising an endogenous, constitutively active G protein coupled orphan receptor and a G protein; b) determining, by measurement of the compound efficacy at said contacted receptor, whether said compound is an inverse agonist, a partial agonist or an agonist of said receptor.

In dependent claims 8 and 9, the GPCR can be GPR6.

In dependent claim 10, the G protein can be Gs.

In dependent claim 11 the Gs protein can be Gsα.

Claim 12, 15 and 16 are directed to a method for directly identifying a candidate compound as a compound selected from the group consisting of an inverse agonist, a partial agonist and an agonist, to an endogenous, constitutively active G protein coupled orphan receptor, comprising the steps of: a)contacting a candidate compound with GPCR Fusion protein, said Fusion Protein comprising an endogenous, constitutively active G protein coupled orphan receptor and a Gsα protein; b) determining, by

measurement of the compound efficacy at said contacted receptor, whether said compound is an inverse agonist, a partial agonist or an agonist of said receptor.

In dependent claims 13 and 14, the GPCR can be GPR6.

In dependent claim 10, the G protein can be Gs.

In dependent claim 11 the Gs protein can be Gsα.

Applicant has asserted utilities for the specifically claimed invention of claims 1-4 and 8-16. For example, the specification at page 1 asserts the invention relates to, "constitutively active G protein-coupled receptors for which the endogenous ligand is known, and most particularly to use of such receptors for direct identification of candidate compounds via screening, partial agonists or inverse agonists to such receptors". The fundamental insight underlying the present invention is the recognition that the constitutively activated orphan receptor/G protein fusion complex can be used to directly identify lead compounds which affect receptor activity and the method of this invention provides a means for discovering modulators of receptor function without the need for any knowledge of the endogenous ligand. The specification discloses, "The pursuit of an endogenous ligand for an orphan receptor can take several years and cost millions of dollars. Furthermore, and given that there are an estimated 2,000 G protein-coupled receptors in the human genome, the majority of which being orphan receptors, the traditional dogma castigates a creative approach to the discovery of therapeutics to these receptors", page 3. Also stated, "For some orphan receptors, it will be apparent to those in the art that there is an understanding of the distribution of such receptors

within, e.g., a human, or associated with a disease state. However, for many orphan receptors, such information is not known, or will not be known", pages 28 and 29.

Orphan receptors by definition are endogenous receptors for which the endogenous ligand specific for that receptor has not been identified or is not known (see page 12). The specification also suggests that constitutively activated G protein coupled cell surface orphan receptors can be used to identify compounds having varying degrees of agonistic activity to said receptors. Binding of ligand to a G protein coupled cell surface orphan receptors results in its interaction with specific G-proteins which in turn results in the activation of various the second messenger G protein couples systems. The methods of instant invention require the production or isolation of constitutively activated G protein coupled cell surface orphan receptors, identifying the G-protein that interacts with said receptor, producing a fusion protein and determining compound efficacy, possibly by unknown second messenger effects

Because an orphan receptor, does not have, by definition, a corresponding endogenous ligand that is known, the specification nor the art of record disclose the function of orphan receptors, the proteins they modulate and their effects on specific disease states. Similarly, constitutively activated orphan receptors have no known function. Thus the corresponding asserted utilities are essentially methods of identify lead compounds which affect constitutively activated orphan receptor activity, which does not define a "real world" context of use. Therefore identifying compounds that interact with orphan receptors would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use. Since neither the

specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the claimed method of identifying compounds having activity of inverse agonist or agonist activity, further experimentation is necessary to attribute a utility to constitutively activated orphan receptors and to the compounds that bind the constitutively activated orphan receptors.

Therefore, since neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the orphan receptors or the compounds identified the claimed method, further experimentation is necessary to attribute a utility to the claimed compounds and to the orphan receptors used to identify said compounds. The instant application does not disclose the biological role of the class of orphan receptors or their significance. After further research, a specific and substantial credible utility might be found for the orphan receptors and the compounds identified by claimed method. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete.

The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-tumor activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the

intended definition of "useful" as it appears in 35 U.S.C. §101, which requires that an invention must have either an immediately apparent or fully disclosed "real world" utility. The court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

Claims 1-4 and 8-16 are drawn to a method of use of orphan receptors with, as yet, undetermined function or biological significance. There is no evidence of record or any line of reasoning that would support a conclusion that the wide class of orphan receptors used in the method of the instant application was, as of the filing date, useful for diagnosis, prevention, and treatment of disease, etc. Until some actual and specific significance can be attributed to the orphan receptor, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention and the compounds identified by said method. Thus, there was no immediately apparent or "real world" utility as of the filing date.

The family of GPCR orphan receptors may have diverse effects and bind a diverse number of ligands. The family of proteins having GPCR like domains have different levels of expression, and play roles in the pathogenesis of various diseases. Although the family of receptor proteins having GPCR like domains may share some common structural motifs, various members of the family may have different sites of action and different biological effects. In the absence of knowledge of the ligand for

orphan receptor or the biological significance of this protein, there is no immediately evident patentable use. To employ GPCR orphan receptors in any of the disclosed methods would clearly be using it as the object of further research. Such a use has been determined by the courts to be a utility which, alone, does not support patentability. Since the instant specification does not disclose a credible "real world" use for the orphan receptor, then the claimed invention as disclosed does not meet the requirements of 35 U.S.C. §101 as being useful.

In conclusion, the utilities asserted by Applicant are not specific or substantial. Since no specific function of the orphan receptors used in instant invention is known, and the hypothesized function can only be based entirely on conjecture from homologous polypeptides, the asserted utilities are not specific to the individual orphan receptors, but rather are based on family attributes. Neither the specification nor the art of record disclose any instances where disorders can be effected by interfering with the activity using the orphan receptors encompassed by the methods claimed. Thus the corresponding asserted utilities are essentially methods of using orphan receptors as targets for drug discovery which does not define a "real world" context of use. Testing for compounds that interact with orphan receptors which may be implicated in an unspecified, undisclosed disease or condition would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use. Since neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the orphan receptors or compounds identified by claimed method, and that interact with orphan receptors, further

experimentation is necessary to attribute a utility to the claimed method. See Brenner v. Manson, 383 U.S. 519, 535–36, 148 USPQ 689, 696 (1966) (noting that "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing", and stated, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."). Further since the orphan receptors or the compounds that bing said orphan receptors are not supported by either a specific and substantial asserted utility or a well established utility, it follows that the methods of using orphan receptors are also not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above

8. Claims 1-4 and 8-16 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Since neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the orphan receptors and compounds that bind orphan receptors, further experimentation is necessary to attribute a utility to the claimed method of using the orphan receptors ,and to the compounds identified by claimed method. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

Claim Rejections, 35 U.S.C. 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103 (c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 and 8-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seifert et al (IDS, Ref., J. Biol.. Chem, 1998, Vol 273, No. 9, pages 5109-5116 in view of Scheer et al (IDS, Ref., J. of receptor and Signal Transduction Research, 1997, Vol 17, pages 57-73) and further in view of Song et al (IDS, Ref., Genomic 1996, Vol.28, pages 347-349), Bertin et al (IDS, Ref., Proc. Natl. Acad. Sci. USA, 1994,

Vol.91, pages 8827-8831) and Wise et al (IDS, Ref., J. Biol. Chem, 1997, Vol 272, No. 39, pag 24673-24678).

Claims 1-4 are directed to a method for directly identifying a candidate compound as a compound selected from the group consisting of an inverse agonist, a partial agonist and an agonist, to an endogenous, constitutively active G protein coupled orphan receptor, comprising the steps of: a)contacting a candidate compound with GPCR Fusion protein, said Fusion Protein comprising an endogenous, constitutively active G protein coupled orphan receptor and a G protein; b) determining, by measurement of the compound efficacy at said contacted receptor, whether said compound is an inverse agonist, a partial agonist or an agonist of said receptor.

In dependent claims 8 and 9, the GPCR can be GPR6.

In dependent claim 10, the G protein can be Gs.

In dependent claim 11 the Gs protein can be Gsα.

Claim 12, 15 and 16 are directed to a method for directly identifying a candidate compound as a compound selected from the group consisting of an inverse agonist, a partial agonist and an agonist, to an endogenous, constitutively active G protein coupled orphan receptor, comprising the steps of: a)contacting a candidate compound with GPCR Fusion protein, said Fusion Protein comprising an endogenous, constitutively active G protein coupled orphan receptor and a Gsα protein; b) determining, by measurement of the compound efficacy at said contacted receptor, whether said compound is an inverse agonist, a partial agonist or an agonist of said receptor.

In dependent claims 13 and 14, the GPCR can be GPR6.

In dependent claim 10, the G protein can be Gs.

In dependent claim 11 the Gs protein can be Gsα.

Seifert discloses a method for directly identifying a candidate compound as a compound selected from the group consisting of an inverse agonist, a partial agonist and an agonist, to an endogenous, constitutively active G protein coupled β_2-adrenoreceptor (β_2-AR) , comprising the steps of: a)contacting a candidate compound with GPCR Fusion protein, said Fusion Protein comprising an endogenous, constitutively active G protein coupled receptor (β_2-AR) and a Gsα protein (Gsα_L); b) determining, by measurement of the compound efficacy at said contacted receptor, whether said compound is an inverse agonist, a partial agonist or an agonist of said receptor (Abstract, experimental procedures). Further, Seifert provides motivation for applying the approach used in making the G protein coupled β_2-adrenoreceptor/Gsα protein Fusion protein construct, used for measurement of the compound efficacy, to study other G protein coupled receptors. The following statements provide said motivation:

a) "Properties of constitutive activity are generally associated with GPCR function, and little is known about the ability of different G-proteins to influence the efficacy and potency of ligands", (page 5109, second column, first paragraph),

b) "To facilitate the examination of receptor/Gprotein interaction we constructed fusion protein DNAs"---- "and expressed the fusion proteins in Sf9 cells" (page 5110, column 1, second paragraph),

c) "Functional interactions between GPCRs and G-proteins are strongly influenced by their relative expression levels",---" to circumvent this problem, we constructed fusion proteins", (of constitutively active G protein coupled orphan receptor (β_2-AR) and a Gsα protein), "thereby guaranteeing a defined stoichiometry of receptor to G-protein and increasing the efficiency of receptor/G-protein coupling", (page 5114, Discussion),

d) "Because the overall properties of β_2-AR and a Gsα protein and their interaction were not changed as a result of fusion, this approach may be applied to a broad variety of receptors and G-proteins to uncover subtle differences in the interaction of closely related G-protein α-subunits with GPCRs", (page 5115, column 2, last paragraph)

Seifert does not teach the constitutively active G protein coupled receptor is a constitutively active G protein coupled orphan receptor or GPR6.

Scheer provides further motivation for studying constitutively active G protein coupled receptor and discloses, "Mutations of G protein-coupled receptors can increase their constitutive (agonist-independent) activity. Some of these mutations have been artificially introduced by site-directed mutagenesis, others occur spontaneously in human diseases. The analysis of constitutively active G protein-coupled receptors has provided important information about the molecular mechanisms underlying receptor activation and drug action" (see abstract.

Song discloses constitutively active G protein coupled receptor GPR6 (see abstract).

Bertin and Wise provide further motivation for studying other G protein coupled receptor:

Bertin discloses the construction o G protein coupled receptor (β_2-AR) and a Gsα protein construct and state, "Such receptorGsα fusion proteins may help to elucidate the complex interaction between members of signaling pathways and may also constitute a useful tool for studying the effects of single effector activation" (page 8827, abstract).

Wise discloses the construction and expression of chimeric fusion protein between α_{2a}-adrenoreceptor and Gi protein to study ligand interaction and state "These studies demonstrate the general utility of generating fusion proteins to examine receptor regulation of G-protein function", (page 24673, Abstract.

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to use the method of Seifer for directly identifying an inverse agonist, a partial agonist and an agonist, to an endogenous, Fusion Protein comprising an endogenous constitutively active G protein coupled β_2-adrenoreceptor (β_2-AR) and apply this method to construct Fusion Protein comprising an endogenous, constitutively active G protein coupled orphan receptor, disclosed by Song, and a Gsα protein to determine, by measurement of the compound efficacy at said contacted receptor, whether said compound is an inverse agonist, a partial agonist or an agonist of said receptor because the method of Seifer may be applied to a broad variety of receptors and G-proteins to uncover subtle differences in the interaction of closely related G-protein α-subunits with GPCRs. The ordinary artisan would have been motivated to use the Fusion Protein construct and method of Seifert et al to measure

the compound efficacy at contacted receptor, to determine whether said compound is an inverse agonist, a partial agonist or an agonist of said receptor because the method of Seifer may be applied to a broad variety of receptors and G-proteins, including orphan receptor GPR6, to uncover subtle differences in the interaction of closely related G-protein α-subunits. Further motivation to substitute other G-protein coupled receptors, which include orphan receptors, is provided by Scheer, Bertin and Wise, who generally state that methods using receptor-Gsα fusion proteins may help to elucidate the complex interaction between members of signaling pathways

No claim is allowed.

Advisory

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 571-272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nirmal S. Basi
Art Unit 1646

GARY B. NICKOL, PH.D.
SUPERVISORY PATENT EXAMINER
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